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DIMETHYLHEPTYL-DELTA 6a-10a-TETRAHYDRO-CANNABINOL: EFFECTS AFTER PARENTERAL ADMINISTRATION TO MAN

Frederick R. Sidell, et al

**Edgewood Arsenal
Edgewood Arsenal, Maryland**

December 1972

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6 α -10 α -TETRAHYDROCANNABINOL:
EFFECTS AFTER PARENTERAL ADMINISTRATION TO MAN

by

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John E. Pless, M.D.

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Medical Research Division
Biomedical Laboratory

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The eight optical isomers of dimethylheptylpyran as the acetate ester were administered parenterally to normal subjects. The main effect was hypotension which was most prominent when the subjects stood. In the doses used, isomers 2 and 4 (and their mixtures) were the only ones possessing biological activity. Doses of 1 to 2 μ g/kg produced a pronounced and prolonged orthostatic hypotension. A resting tachycardia occurred with isomer 4. Symptoms were those related to hypotension, plus dry mouth, thirst and hunger, sleepiness, and irritated eyes with conjunctivitis suggesting a mild marihuana syndrome.

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The volunteers in these tests are enlisted US Army personnel and inmates of a penal institution (Holmesburg Prison, Holmesburg, Pennsylvania). These tests are governed by the principles, policies, and rules for medical volunteers as established in AR 70-25 and the Declaration of Helsinki.

Task 1W062116AD2103

DEPARTMENT OF THE ARMY
HEADQUARTERS, EDGECOOL ARSENAL
EDGECOOL ARSENAL, MARYLAND 21010

FOREWORD

The work described in this report was authorized under Project/Task 1W062116AD2103, Medical Effects of Chemical Agents; Clinical Evaluation of Chemical Agents. This work was started in June 1964 and completed in October 1969.

The volunteers in these tests are enlisted US Army personnel and inmates of a penal institution (Holmesburg Prison, Holmesburg, Pennsylvania). These tests are governed by the principles, policies, and rules for medical volunteers as established in AR 10-25 and the Declaration of Helsinki.

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DIGEST

The eight optical isomers of dimethylheptylpyran as the acetate ester were administered parenterally to normal subjects. The main effect was hypotension which was most prominent when the subjects stood. In the doses used, isomers 2 and 4 (and their mixtures) were the only ones possessing biological activity. Doses of 1 to 2 μ g/kg produced a pronounced and prolonged orthostatic hypotension. A resting tachycardia occurred with isomer 4. Symptoms were those related to hypotension, plus dry mouth, thirst and hunger, sleepiness, and irritated eyes with conjunctivitis suggesting a mild marihuana syndrome.

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DIMETHYLHEPTYL-DELTA 6a-10a-TETRAHYDROCANNABINOL: EFFECTS AFTER PARENTERAL ADMINISTRATION TO MAN

I. INTRODUCTION.

In an extensive series of investigations several decades ago, Adams *et al.*^{1,2} synthesized a number of compounds differing from the naturally occurring tetrahydrocannabinol (THC) by the position of the double bond in the first ring. The natural material is unsaturated in the Δ^9 position [by the formal, dibenzopyran numbering system (or the Δ^1 position, terpene numbering)], whereas the synthetic compounds had the double bond in the Δ^{6a-10a} [dibenzopyran numbering (or Δ^3 position, terpene numbering)] (figure 1). The side chain of the natural product is an n-amyl group.

The potency of these synthetic compounds varied considerably depending on this side group;¹⁻³ the n-hexyl homolog was found to be more potent than the n-amyl (which corresponds to the side chain of the natural product) and the former (parahexyl; synhexyl) has been found to produce marihuana-like signs and symptoms in man.^{4,5} However, the most potent homolog was found to be that with a 1',2'-dimethylheptyl group (dimethylheptyl-delta 6a-10a-THC; dimethylheptylpyran; DMHP). DMHP possessed 60-512 times the biological activity of the natural product.¹⁻³

The pharmacology of DMHP in animals has been described.⁶⁻⁸ The most marked effects are hypotension, hypothermia, analgesia, and behavioral changes.

An early clinical trial⁹ indicated that this compound might be useful in the therapy of grand mal epilepsy not readily amenable to treatment by other drugs. Further investigations were terminated because the potency of the available preparation varied from one sample to the next.⁷ As the compound has three asymmetric carbon atoms, it can exist as eight optical isomers, and differing proportions of these isomers in different samples may have been the reason for the inconsistent activity.

¹ Adams, R., MacKenzie, S., and Loewe, S. Tetrahydrocannabinol Homologs with Doubly Branched Alkyl Groups in the 3-Position XVIII. *J. Amer. Chem. Soc.* 70, 664-668 (1948)

² Adams, R., Harfenist, M., and Loewe, S. New Analogs of Tetrahydrocannabinol XIX. *J. Amer. Chem. Soc.* 71, 1624-1628 (1949).

³ Loewe, S. Cannabis-Active Products and Pharmacology of Cannabinols. *Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol.* 211, 175-193 (1950).

⁴ Hollister, L. E., Richards, R. K., and Gillespie, H. K. Comparison of Tetrahydrocannabinol and Synhexyl in Man. *Clin. Pharmacol. Ther.* 9, 783-791 (1968).

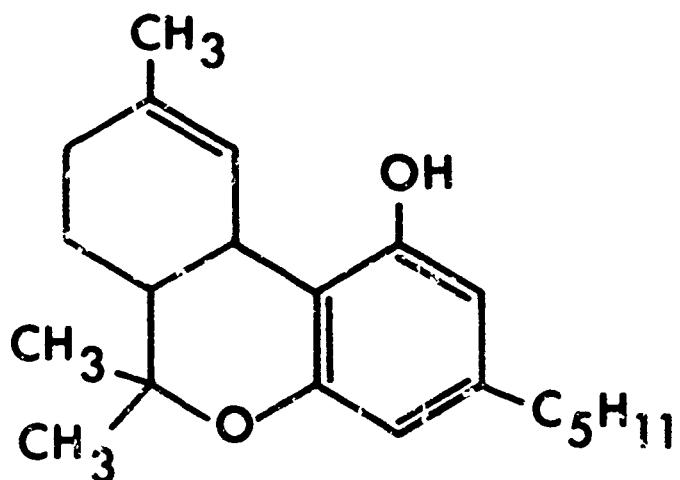
⁵ Williams, E. G., Himmelsbach, C. K., Wilber, A., and Ruble, D. C. Studies on Marihuana and Pyrahexyl Compound. *Pub. Health Rep.* 61, 1059-1083 (1946).

⁶ Dagimanjian, R., and Boyd, E. S. Some Pharmacological Effects of Two Tetrahydrocannabinols. *J. Pharmacol. Exp. Ther.* 135, 25-33 (1962).

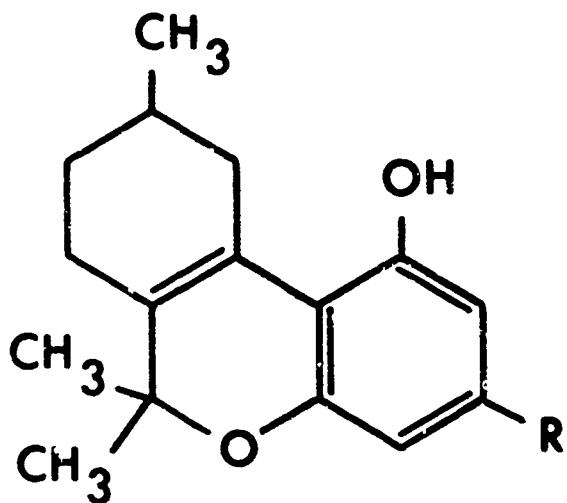
⁷ Hardman, H. F., Domino, E. F., and Seavers, M. H. General Pharmacological Actions of Some Synthetic Tetrahydrocannabinol Derivatives. *Pharmacol. Revs.* 23, 295-315 (1971).

⁸ Domino, E. F., Hardman, H. F., and Seavers, M. H. Central Nervous System Actions of Some Synthetic Tetrahydrocannabinol Derivatives. *Ibid.*, 3:7-336.

⁹ Davis, J. P., and Ramsey, H. H. Antiepileptic Action of Marihuana-Active Substances. *Fed. Proc.* 8, 284-285 (1949).



Δ^9 (OR Δ^1) TETRAHYDROCANNABINOL



Δ^3 (OR Δ^{6a-10a}) TETRAHYDROCANNABINOL

R = C₆H₁₃: SYNHEXYL

R = CH(CH₃)CH(CH₃)C₅H₉: DIMETHYLHEPTYLPYRAN

Figure 1. Structure of Δ^9 -THC (Natural Product) and Two Synthetic Congeners Having the Double Bond in the Δ^3 Position

Aaron and Ferguson¹⁰ synthesized these eight isomers and isolated each after conversion into their more stable acetate esters. They also assigned isomer numbers and described the physical chemical characteristics of each isomer.

This report describes the effects in man after parenteral administration of the acetate esters of the eight isomers, the racemic mixture, and a mixture of equal parts of isomers 2 and 4.

II. EXPERIMENTAL.

A. Subjects.

Subjects were US Army enlisted men or inmates of a penal institution * All volunteered specifically for this study after the test procedures and possible effects were explained to them. They were not told the relationship of the drug to marihuana. The possibility that some had been users of marihuana cannot be excluded; although, at the time of the study (1964-1967), marihuana use was not as prevalent as it is now.

All subjects had a thorough physical examination and laboratory studies (electrocardiogram, chest X-ray, red cell and total and differential white blood cell counts, urinalysis, bilirubin, serum glutamic oxaloacetic transaminase, etc.) and were felt to be within normal limits on the Minnesota Multiphasic Personality Inventory (MMPI) and were judged to give normal responses on a psychiatric interview. The criteria on the MMPI were not quite as stringent** for the prison inmates, but there were no subjects with a markedly deviant profile.

The ward and test procedures and medical supervision were similar for the military and inmate subjects.

Several subjects who had no effect from their first test were used a second time at another dose. In each case, they again had no effects.

B. Drug.

The compounds were the materials described by Aaron and Ferguson.¹⁰ They were dissolved in propylene glycol (1 mg/ml) initially and further dilutions in propylene glycol were made daily. The material was assayed chemically at the beginning and end of each series of studies and no deterioration was noted.

The racemic mixture was studied first, then the 2-4 mixture, then isomer 2 and isomer 4 individually. These were given intravenously. Since marked activity was found with small amounts of these four preparations, it was arbitrarily decided to stop investigation of the other isomers at a dose of 10 µg/kg. These isomers (1,3,5,6,7, and 8) were given intramuscularly.

* Holmesburg Prison, Holmesburg, Pennsylvania. These tests were conducted under Edgewood Arsenal contract DAAA15-70-C-0324.

** For military personnel, all "t" scores were under 70; for the inmates, no score was above 80.

¹⁰ Aaron, H. S., and Ferguson, C. P. Synthesis of the Eight Stereoisomers of a Tetrahydrocannabinol Congener. *J. Org. Chem.* 33, 684-689 (1968).

Twenty-five subjects were used as placebo controls and received only the vehicle, propylene glycol. Neither they nor the observers (except the physician in charge) knew they received placebos and the test procedures were identical to those for subjects receiving the actual drug. These subjects were tested with those that received the mixtures, isomer 2, and isomer 4. Doses and number of subjects for each dose of each compound are shown in table I.

C. Methods.

An appropriate number of pretest baseline measures of cognitive function (see below) were obtained several days before the test.

The subjects entered the test ward the evening before the test and several baseline measures of physiological and cognitive function were obtained. Upon awakening and after eating a light breakfast, the subjects took further baseline tests.

After they received the drug, the subjects were free to be up and around the ward, converse, watch television, etc., but they lay supine for 10 minutes preceding measurement of blood pressure and heart rate. All tests lasted 24 hours or longer as indicated. While on the ward, the subjects were under the constant observation and care of thoroughly trained nurses and technicians who, in turn, were under the supervision of a physician.

1. Measures.

a. Physiological.

Heart rate and blood pressure were measured at each test period with the subject in the supine position, after standing 1 minute, and 5 minutes later while still erect. In the early part of the study, this was preceded by three to five sets of baseline measures the morning of the test; during most of the study, eight such sets of control measures, 10 minutes apart, were used.

Pupil size was estimated with a disc pupillometer using a constant light source at each test period. This was preceded by three control measures before the test began.

Axillary temperature was measured twice before the test and every 4 hours after drug administration.

b. Cognitive.

The Number Facility (NF) test, a 3-minute addition task, was the only measure of intellectual function used throughout the study. The baseline score was the average of the 5 highest scores among 25 trials given in the days preceding the test (including two trials the evening before and three trials the morning of the test.) In the early series, the mean of the 3 highest scores of 10 pretest trials was used but, considering the results, this methodological difference is felt to be insignificant. Results are expressed as the percentage of this baseline.

Table I. Isomers, Doses, and Number of Subjects

Racemic mixture		Isomers								Placebo
		2-4 (mixture)		2		4		1, 3, 5, 6, 7, 8*		
Dose	No.	Dose	No.	Dose	No.	Dose	No.	Dose	No. per each isomer	
μg/kg		μg/kg		μg/kg		μg/kg		μg/kg		
0.5	2	0.5	2	0.5	3	0.5	2	1.0	2	
0.7	2	1.0	2	0.7	2	0.7	2	1.4	2	
1.0	4	1.25	4	1.0	3	1.0	2	2.0	2	
1.4	4	1.5	4	1.4	2	1.4	2	2.8	2	
2.0	1	1.75	8	2.0	2	2.0	2	3.9	2	
2.8	2	2.0	7	2.4	2	2.8	2	5.4	2	
3.4	2	2.25	4	2.8	2	4.8	2	7.5	2	
4.0	2	2.55	6			5.8	2	10.5	2	
4.9	2									
5.9	3									
6.5	2									
7.2	2									
8.3	5									
Total	33		37		16		16		16	25
									(Total 96)	
										Grand Total 223

* Sixteen subjects for each isomer.

Additional psychological and performance measures were employed on the study of the last six isomers. Since all results with these isomers (1,3,5,6,7, and 8) were negative, the details will not be presented.

c. Clinical.

Frequent observations were made and recorded by the nurses and physicians. A Behavior Check List (BCL), listing 50 signs or symptoms most commonly noted in subjects receiving centrally active drugs, was completed by the observer at each test period. In addition, before his discharge each subject filled in a Symptom Check List (SCL) and wrote a resume of his test experience. All these recorded observations, as well as results of frequent examinations by the physicians, form the basis of the clinical descriptions.

2. Laboratory.

Laboratory tests including red cell and total and differential white blood cell counts, bilirubin, serum glutamic oxaloacetic transaminase, alkaline phosphatase, and urinalysis were performed on each subject the morning of the study at 24 or 48 hours and 7 to 10 days later. All were negative.

D. Data Analysis.

For each test measure (heart rate, blood pressure, Number Facility, etc.), the number of positive reactors in each drug group was compared to the number in the placebo group using the chi-square test. A similar comparison was made for each sign or symptom.

A positive reactor was an individual who had two consecutive post-drug tests outside the range of the mean and 2 standard deviations (SD) of all his pre-drug scores. Using blood pressure as an example, in 3 of the 25 placebo subjects the mean of two consecutive lowest post-“drug” scores was below their pre-“drug” mean minus 2 SD’s.

In addition, dose-response regressions were calculated for all measures. In each case, when the chi-square statistic was not significant ($P > 0.05$), the slope of the regression line was close to zero.

All blood pressure measurements are represented as the mean, defined as the diastolic plus one-third of the difference between the systolic and diastolic. The blood pressure was considered to be zero when no reading could be obtained either audibly or by palpation. Most of the time “zero” readings were recorded when the subject was quite symptomatic from hypotension and was allowed to lie down after a brief, unsuccessful palpitory effort to find a pulse.

In constructing the figures, the control blood pressure used was the mean of the baseline values minus 2 SD’s, except in the serial representations of data where the mean baseline value is shown.

III. RESULTS.

A. Clinical and Physiological.

Table II summarizes the effects. Negligible effects were noted from isomers 1, 3, 5, 6, 7, and 8 and the data are not shown.

The most prominent effect was hypotension which was more marked when the subjects stood. The magnitude (figures 2, 3, 4, and 5) and duration (figures 2, 6, 7, and 8) of the orthostatic hypotension were dose related in all four groups, but the decrease in supine blood pressure and the duration of this decrease were related to dose only for the racemic mixture. The response varied considerably from subject to subject, as shown.

Figure 9 shows two extremes of response. One subject had a slight but definite orthostatic hypotension for about 8 hours; the other had a marked orthostatic hypotension for about 24 hours. Figure 10 shows the mean response of the group receiving the highest dose of the racemic mixture and is typical of the high dose groups.

Tachycardia always accompanied the hypotension when the subject stood, but resting tachycardia was less common. Subjects who had hypotension did not necessarily have resting tachycardia; e.g., one subject with prolonged and marked orthostatic hypotension had a resting heart rate within his control limits. Tachycardia was most prominent after isomer 4 and in the mixture of isomers 2 and 4. The magnitude of the tachycardia was generally about 5 to 15 beats per minute above the control limits and it usually lasted 3 to 5 hours. A resting bradycardia was noted in a number of subjects, but this finding was not statistically different from that of the placebo group.

When symptoms occurred, they usually started 1 to 2 hours after drug administration and lasted for 2 to 6 hours. Only three subjects had a notable mental effect (isomer 2, doses of 1.0, 2.0, and 2.0 μ g/kg), and this was a mild euphoria with an uncontrollable urge to laugh. During this period, these subjects had a moderate (25% to 30%) decrement on their NF scores but had no other evidence of mental impairment.

The most noticeable objective effect was conjunctival injection which usually accompanied the complaint of "irritated eyes." Although most of the symptoms were dose related, this was more common in the middle dose ranges.

Dizziness and lightheadedness accompanied the hypotension and are not shown separately in the table.

NF scores were not different from those of the placebo group, nor was there a dose-response relationship for any isomer (or mixture).

No temperature changes were noted.

Table II. Symptoms and Physiological Changes

Symptoms and physiological changes	Placebo	Racemic mixture	2-4 Mixture	Isomer 2	Isomer 4
<u>Symptom</u>					
Dry mouth	1	6	24 ^{xx}	7 ^x	5 ^x
Headache	1	1	3	6 ^x	7 ^x
Drowsy/lethargic	3	3	12	10 ^{xx}	6 ^x
Irritated eyes	0	0	13 ^{xx}	4 ^x	2
Thirst	0	3	0	6 ^{xx}	5 ^x
Hunger	0	0	0	5 ^x	0
Blurred vision	0	3	0	5 ^x	2
Nausea	1	3	5	2	5 ^x
Euphoria (laughter)	0	0	0	3*	0
<u>Physiological changes</u>					
Hypotension					
Supine	3	10	13*	9 ^x	9 ^x
Standing (1 min)	6	19 ^x	31 ^{xx}	13 ^{xx}	11 ^x
Standing (5 min)	5	23 ^{xx}	31 ^{xx}	12 ^{xx}	12 ^{xx}
Tachycardia	6	13	20 ^x	3	10 ^x
Bradycardia	6	6	13	1	2
Total number of subjects	25	33	37	16	16

* p<0.05, compared to placebo group.

x p<0.01, compared to placebo group.

xx p<0.001, compared to placebo group.

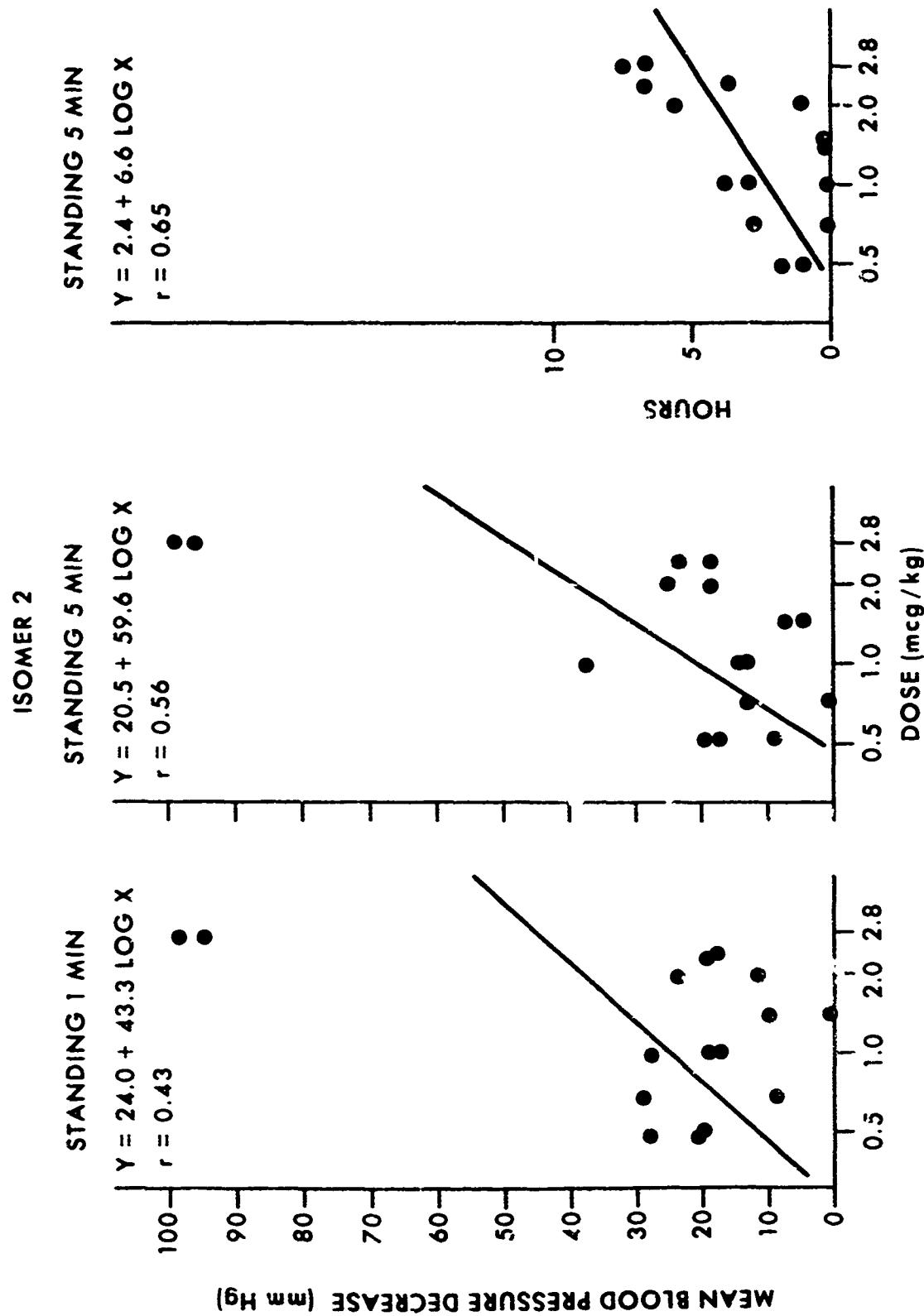


Figure 2. Isomer 2: Mean Blood Pressure Decrease Versus Dose at Two Test Times and Duration of Hypotension Versus Dose for the Test After Standing 5 Minutes (The other regressions had insignificant slopes.)

ISOMER 4

STANDING 1 MIN

$$Y = 17.3 + 25.8 \log X$$

$$r = 0.47$$

MEAN BLOOD PRESSURE DECREASE (mm Hg)

STANDING 5 MIN

$$Y = 24.4 + 21.9 \log X$$

$$r = 0.28$$

DOSE (mcg/kg)

Figure 3. Isomer 4: Mean Blood Pressure Decrease at Two Test Times

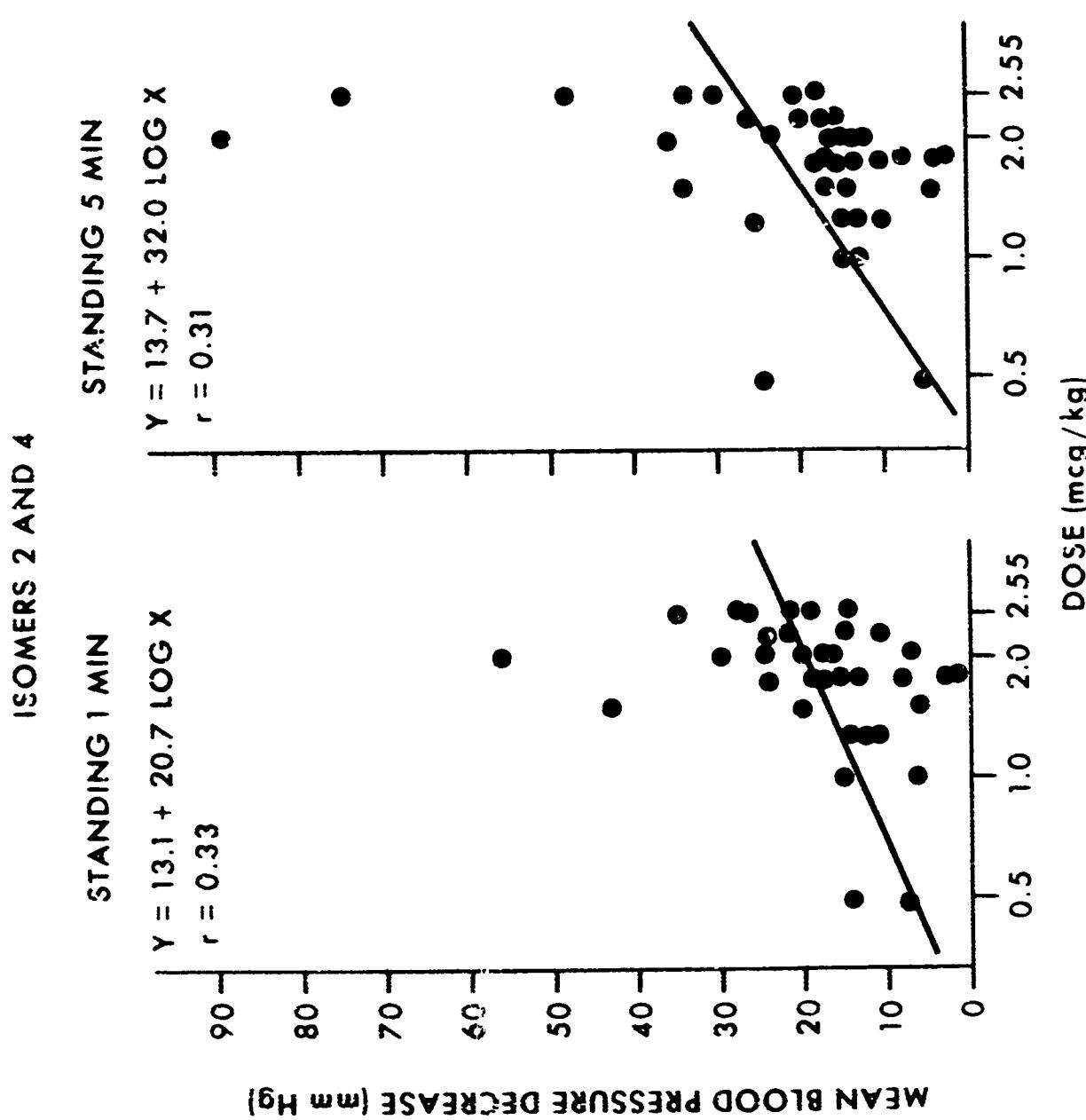


Figure 4 Isomers 2-4 Mixture: Mean Blood Pressure Decrease Versus Dose at Two Test Times

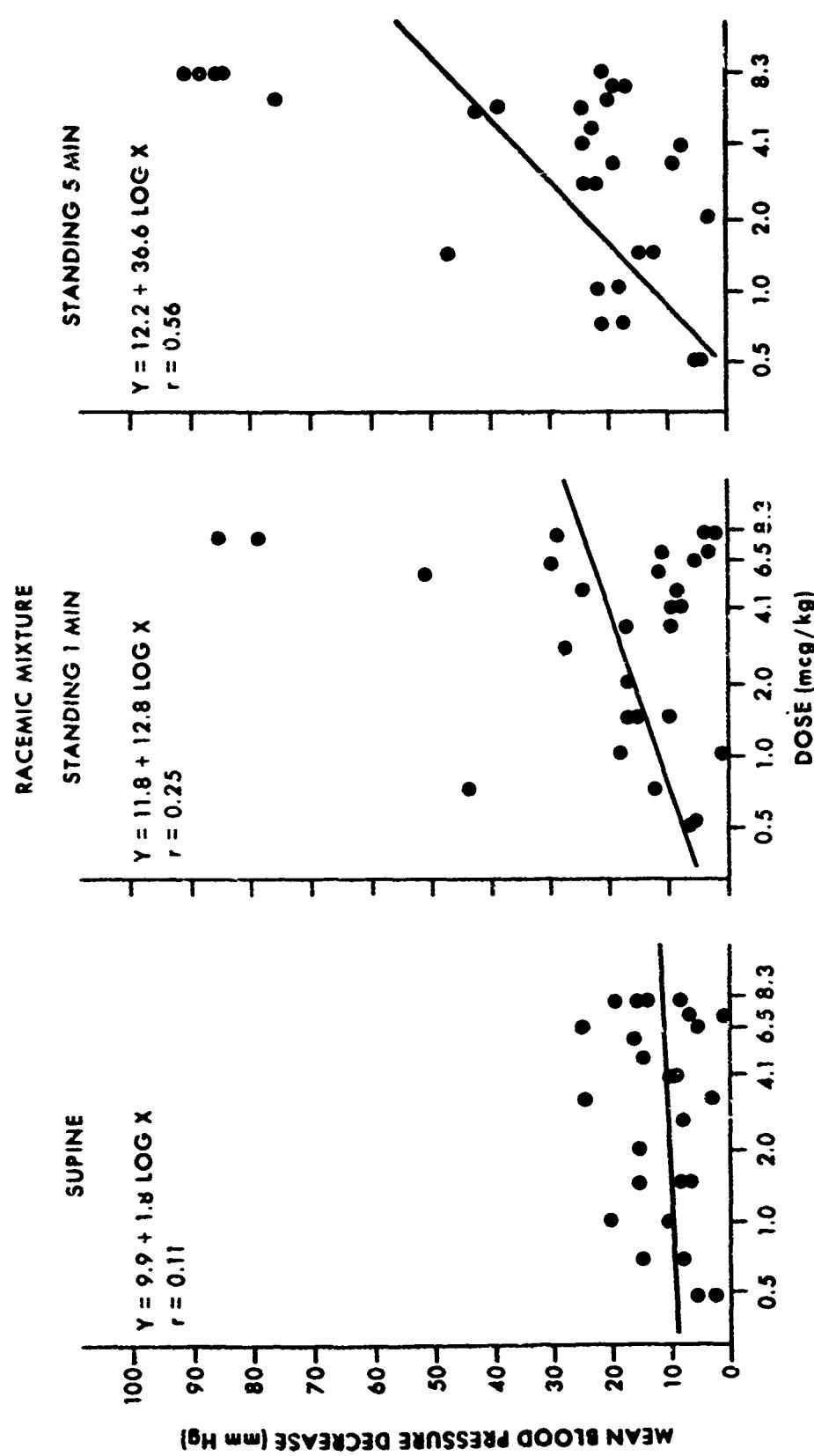


Figure 5. Racemic Mixture: Mean Blood Pressure Decrease Versus Dose at Three Test Times

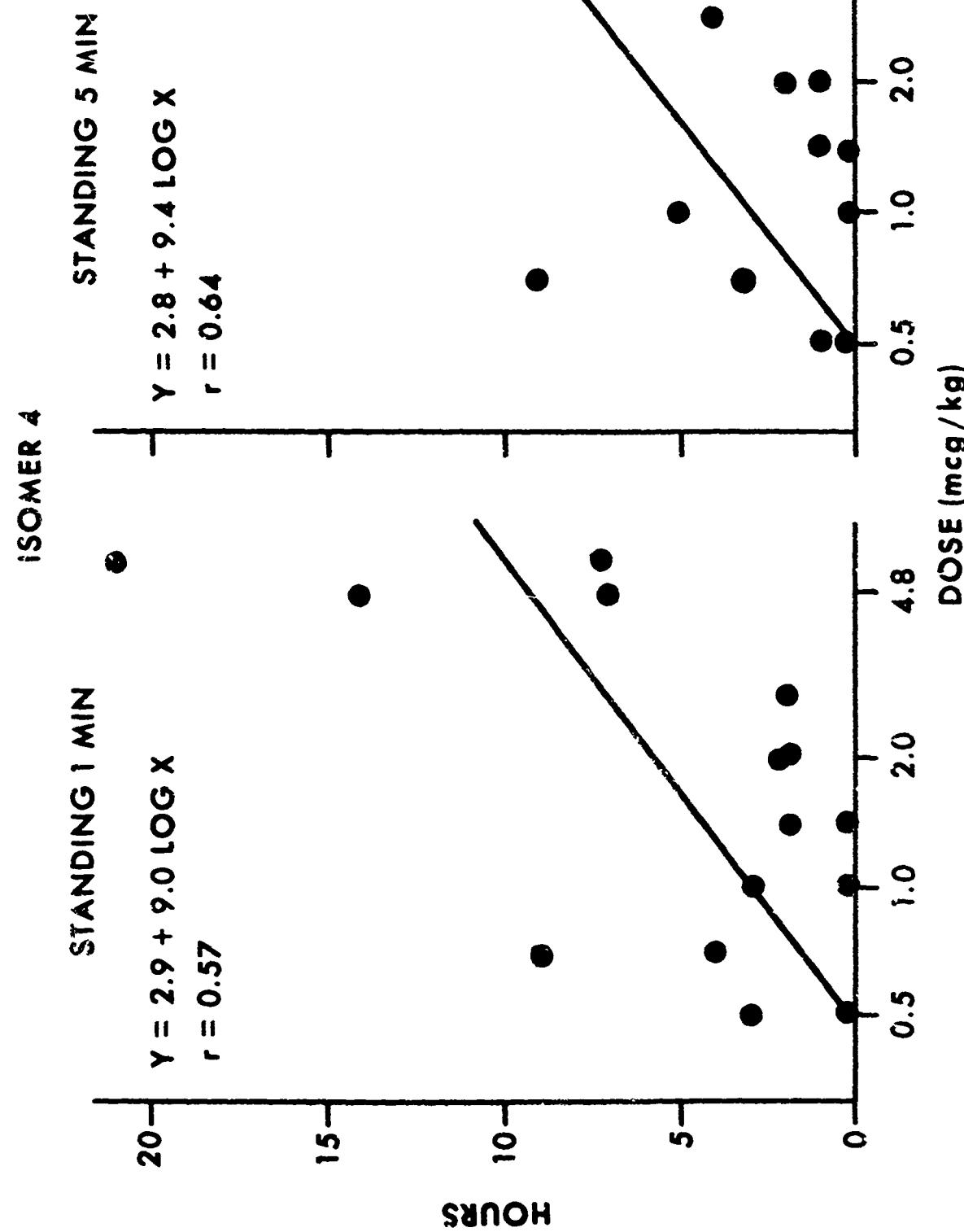


Figure 6. Isomer 4. Duration of Hypotension Versus Dose

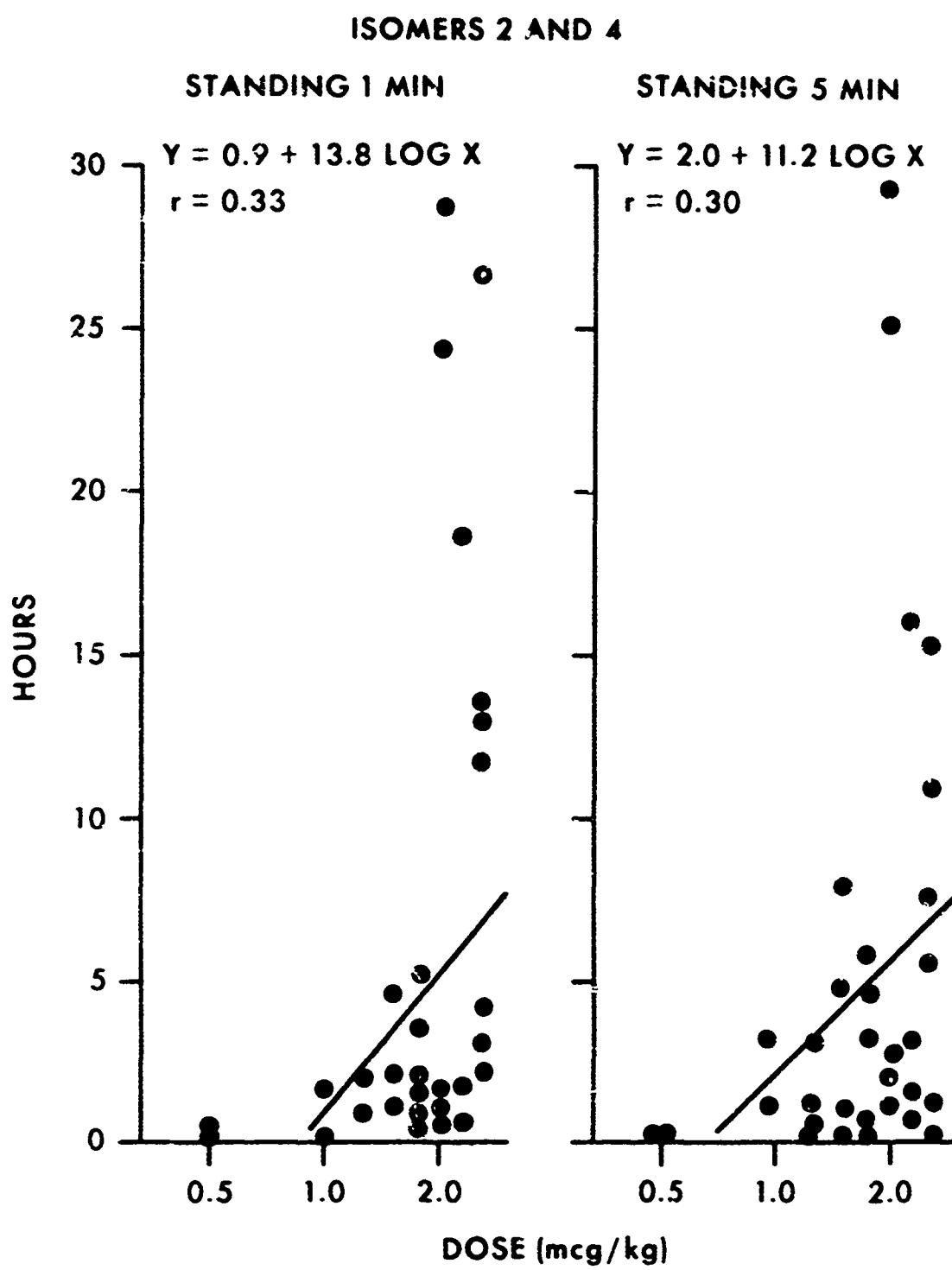


Figure 7. Isomers 2-4 Mixture: Duration of Hypotension Versus Dose

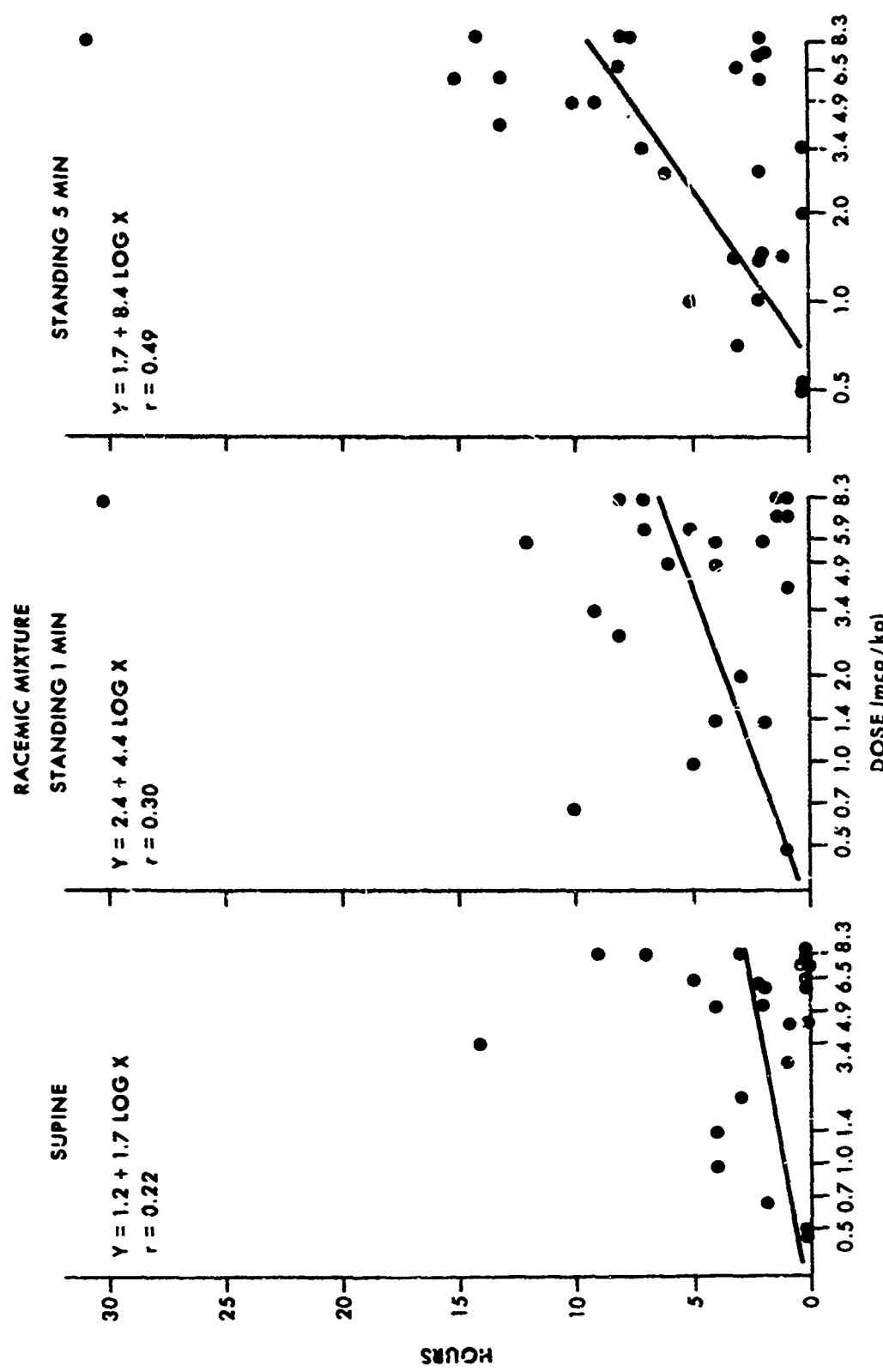


Figure 8. Racemic Mixture: Duration of Hypotension Versus Dose

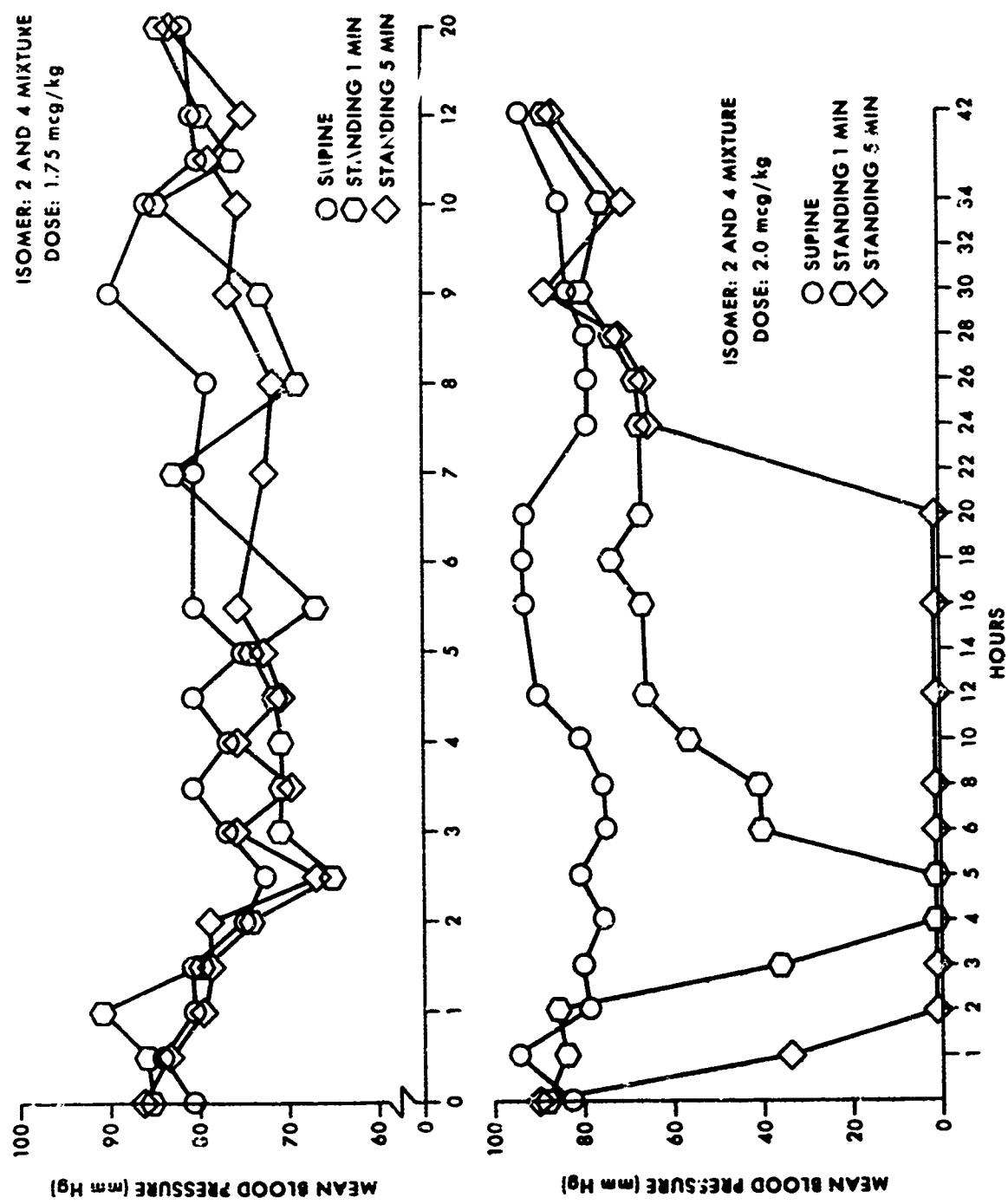


Figure 9. Isomers 2-4 Mixture: Two Typical and Different Responses in Two Subjects
The upper shows a definite although mild orthostatic hypotension; the lower is a severe orthostatic hypotension.

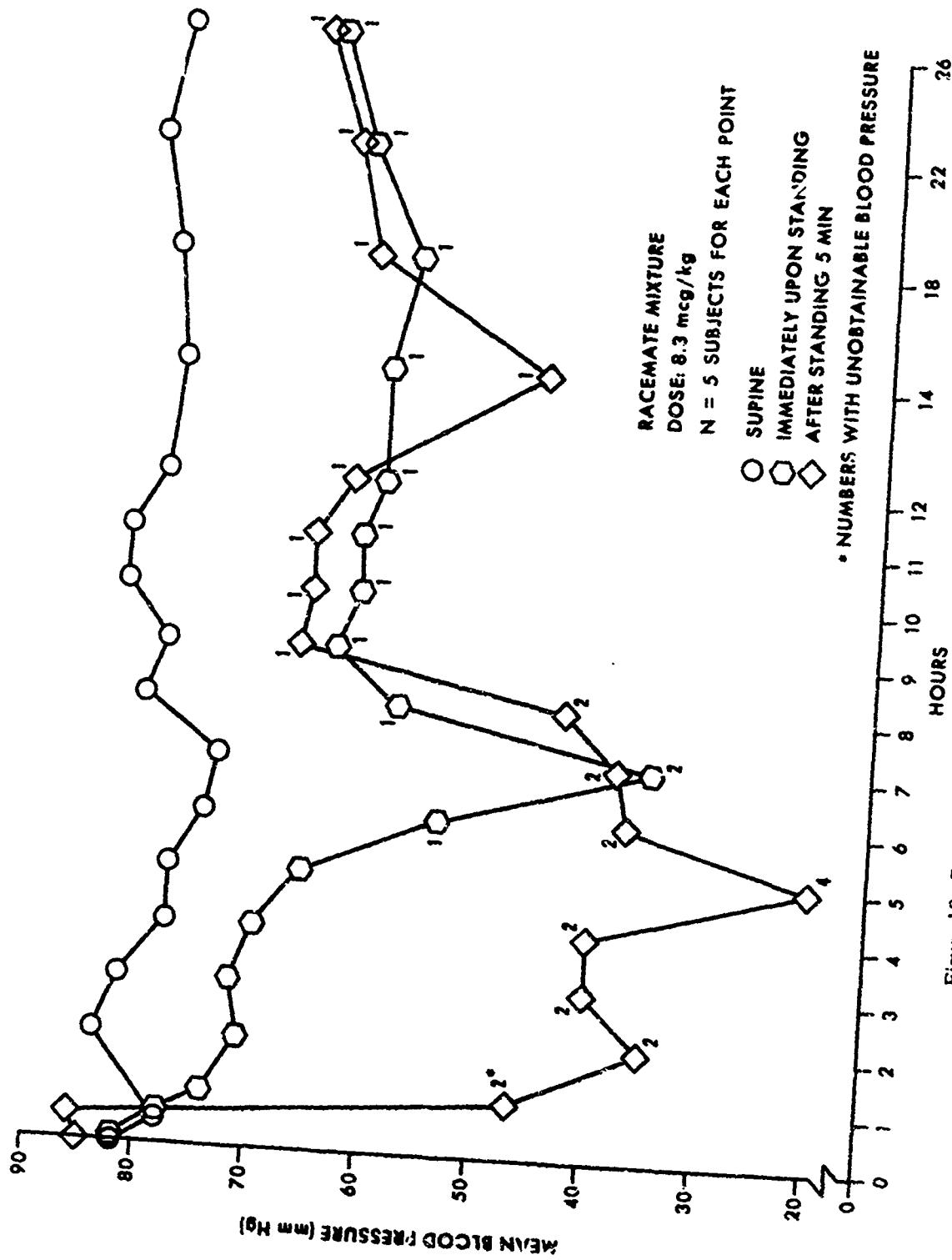


Figure 10. Racemic Mixture: The Mean Response of the Highest Dose Group
When the blood pressure was unobtainable, it was considered to be zero.

B. Therapy.

The sympathomimetic compounds methoxamine hydrochloride and phenylephrine hydrochloride were used to treat the hypotension in eight subjects. A rough dose-response curve was estimated for each subject several days prior to the study by giving him increasing doses of the sympathomimetic compound until a dose which produced a notable increase in blood pressure was reached. This was usually 3 to 5 mg (im) of methoxamine or 0.5 mg (iv) of phenylephrine.

Both compounds were found to adequately reverse the hypotension; the effects of methoxamine lasted 1 to 2 hours whereas the effects of phenylephrine were of shorter duration. Figure 11 shows the serial mean blood pressure values in one subject who twice received methoxamine hydrochloride.

IV. SUMMARY AND DISCUSSION.

Isomers 2 and 4 of the acetate ester of DMHP were found to be extremely potent in producing hypotension, primarily orthostatic, in man.

Although the responses were quite variable from subject to subject, overall doses in the range of 1 to 2 μ g/kg of either isomer caused a decrease in mean orthostatic blood pressure of 20 to 40 mm Hg. The effect on supine blood pressure was less pronounced and ranged from 5 to 10 mm Hg. A mixture of the two, in equal concentrations, produced less than an additive effect, although the marked scatter in response clouds a clear comparison. A mixture of the eight isomers was approximately one-fourth as potent as the individual isomers suggesting that most if not all the activity is due to isomers 2 and 4.

The degree of hypotension varied considerably; e.g., at the highest dose, the racemic mixture produced a 1-minute decrease ranging from 3 and 4 mm Hg to a complete loss of audible blood pressure.

The onset time and duration were less variable. At the high doses, the onset was usually within an hour (figures 9 through 11) and, in some cases, the effect persisted for over 24 hours. More commonly, onset of effects was about 2 to 3 hours after administration and the effects lasted 5 to 10 hours.

The incidence of resting tachycardia in the groups receiving isomer 4 alone and the 2-4 mixture was higher than in the placebo group.

Dagirmanjian and Boyd⁶ and Hartman *et al.*⁷ showed that DMHP produced hypotension in anesthetized cats and dogs, and the latter investigators reported bradycardia in unanesthetized dogs and monkeys. In man, Isbell¹¹ reported tachycardia but no blood pressure changes, whereas Hollister⁴ noted hypotension and tachycardia after Δ^9 -THC. Weil¹² also reported tachycardia in normal subjects after they had smoked marihuana (Δ^9 -THC).

¹¹ Isbell, H., Gorodetsky, C. W., Jasinski, D., Claussen, U., v. Spulak, F., and Korte, F. Effects of (-) Δ^9 -Trans-Tetrahydrocannabinol in Man. *Psychopharmacologia* **11**, 184-188 (1967).

¹² Weil, A. T., Zinberg, N. E., and Nelsen, J. M. Clinical and Psychological Effects of Marihuana in Man. *Science* **162**, 1234-1242 (1968).

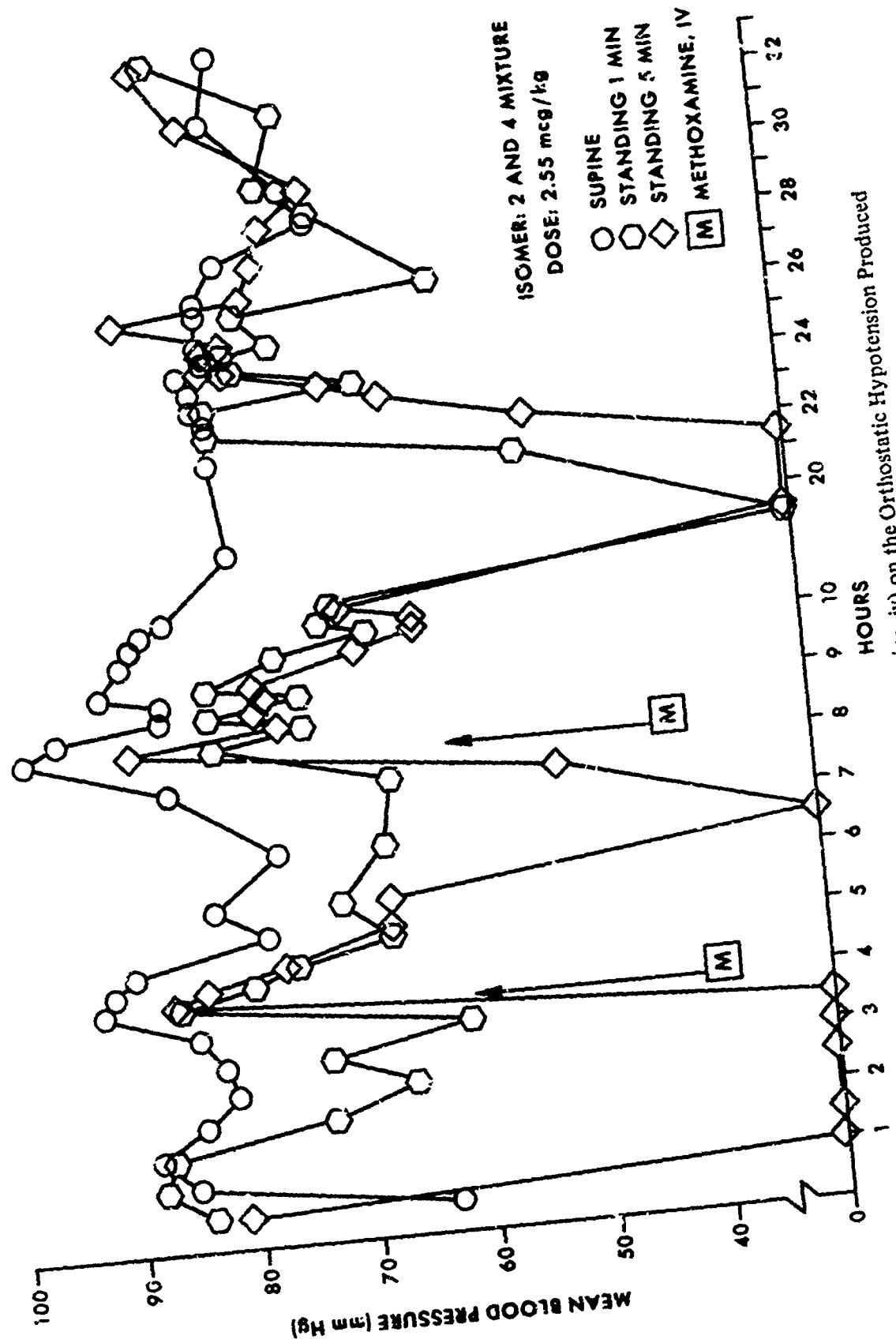


Figure 11. Effect of Therapy (Methoxamine, iv) on the Orthostatic Hypotension Produced by 2.55 μ g/kg of Isomers 2-4 Mixture

The mechanism of the hypotension has not been elucidated despite elaborate investigations.^{6,7} Its response to the sympathomimetics suggests that the mechanism is not α -adrenergic blockade.

The lack of activity of six of the isomers in the doses used may be because they were given intramuscularly. Loewe³ noted for one of the homologs of this series that subcutaneous administration rarely has any documentable effect. However, because in animal tests (visual discrimination in the monkey), isomers 2 and 4 were the most potent of the eight¹³ and because the hypotensive activity of the mixture can be accounted for by isomers 2 and 4, we feel that the other isomers lack activity, at least in the doses used.

The most severe symptoms were those related to hypotension. Thirst, xerostomia, sleepiness, eye irritation with conjunctivitis, and increased hunger were also frequently noted. Three subjects (isomer 2) had mild euphoria associated with a modest decrement on the NF test, but reported no perceptual or other psychic impairments.

This cluster of symptoms is similar to that reported for Δ^9 -THC and synhexyl⁴ and suggests a mild marihuana effect. As Weil *et al.* noted,¹² even at high doses of marihuana naive subjects reported very few subjective effects and did not experience the "high" commonly reported by chronic users. Thus the lack of a full blown syndrome is not unexpected.

The therapeutic potentials of this compound are still relatively unexplored. Their early promise in the treatment of epilepsy might be reexplored using the pure compound or the individual isomers. Hardman *et al.*⁷ have suggested that this might also be beneficial in certain cases of hypertension or hyperthermia, possibilities awaiting clinical trials.

¹³ Mennear, J. H., and Samuel, G. K. Hazleton Laboratories Report No. 28. Contract No. DA-18-108-405-CML-826. Hazleton Laboratories, Falls Church, Virginia. 1962. CONFIDENTIAL Report.

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